

--40. A recombinant polypeptide having the ability to bind to TNF which is encoded by DNA selected from the group consisting of:

A) DNA comprising the sequence:

ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG CTG CCA CTG GTG  
CTC CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA GGG GTT ATT  
GGA CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA GAT AGT  
GTG TGT CCC CAA GGA AAA TAT ATC CAC CCT CAA AAT AAT TCG  
ATT TGC TGT ACC AAG TGC CAC AAA GGA ACC TAC TTG TAC AAT  
GAC TGT CCA GGC CCG GGG CAG GAT ACG GAC TGC AGG GAG TGT  
GAG AGC GGC TCC TTC ACC GCT TCA GAA AAC CAC CTC AGA CAC  
TGC CTC AGC TGC TCC AAA TGC CGA AAG GAA ATG GGT CAG GTG  
GAG ATC TCT TCT TGC ACA GTG GAC CGG GAC ACC GTG TGT GGC  
TGC AGG AAG AAC CAG TAC CGG CAT TAT TGG AGT GAA AAC CTT  
TTC CAG TGC TTC AAT TGC AGC CTC TGC CTC AAT GGG ACC GTG  
CAC CTC TCC TGC CAG GAG AAA CAG AAC ACC GTG TGC ACC TGC  
CAT GCA GGT TTC TTT CTA AGA GAA AAC GAG TGT GTC TCC TGT  
AGT AAC TGT AAG AAA AGC CTG GAG TGC ACG AAG TTG TGC CTA  
CCC CAG ATT GAG AAT GTT AAG GGC ACT GAG GAC TCA GGC ACC  
ACA GTG CTG TTG CCC CTG GTC ATT TTC TTT GGT CTT TGC CTT  
TTA TCC CTC CTC TTC ATT GGT TTA ATG TAT CGC TAC CAA CGG  
TGG AAG TCC AAG CTC TAC TCC ATT GTT TGT GGG AAA TCG ACA  
CCT GAA AAA GAG GGG GAG CTT GAA GGA ACT ACT ACT AAG CCC  
CTG GCC CCA AAC CCA AGC TTC AGT CCC ACT CCA GGC TTC ACC  
CCC ACC CTG GGC TTC AGT CCC GTG CCC AGT TCC ACC TTC ACC  
TCC AGC TCC ACC TAT ACC CCC GGT GAC TGT CCC AAC TTT GCG  
GCT CCC CGC AGA GAG GTG GCA CCA CCC TAT CAG GGG GCT GAC  
CCC ATC CTT GCG ACA GCC CTC GCC TCC GAC CCC ATC CCC AAC  
CCC CTT CAG AAG TGG GAG GAC AGC GCC CAC AAG CCA CAG AGC  
CTA GAC ACT GAT GAC CCC GCG ACG CTG TAC GCC GTG GTG GAG  
AAC GTG CCC CCG TTG CGC TGG AAG GAA TTC GTG CGG CGC CTA  
GGG CTG AGC GAC CAC GAG ATC GAT CGG CTG GAG CTG CAG AAC  
GGG CGC TGC CTG CGC GAG GCG CAA TAC AGC ATG CTG GCG ACC  
TGG AGG CGG CGC ACG CCG CGG CGC GAG GCC ACG CTG GAG CTG  
CTG GGA CGC GTG CTC CGC GAC ATG GAC CTG CTG GGC TGC CTG  
GAG GAC ATC GAG GAG GCG CTT TGC GGC CCC GCC GCC CTC CCG  
CCC CGC CCC AGT CTT CTC AGA TGA

B) DNA comprising the sequence:

GAT AGT GTG TGT CCC CAA GGA AAA TAT ATC CAC CCT CAA  
AAT AAT TCG ATT TGC TGT ACC AAG TGC CAC AAA GGA ACC TAC  
TTG TAC AAT GAC TGT CCA GGC CCG GGG CAG GAT ACG GAC TGC  
AGG GAG TGT GAG AGC GGC TCC TTC ACC GCT TCA GAA AAC CAC  
CTC AGA CAC TGC CTC AGC TGC TCC AAA TGC CGA AAG GAA ATG  
GGT CAG GTG GAG ATC TCT TCT TGC ACA GTG GAC CGG GAC ACC  
GTG TGT GGC TGC AGG AAG AAC CAG TAC CGG CAT TAT TGG AGT  
GAA AAC CTT TTC CAG TGC TTC AAT TGC AGC CTC TGC CTC AAT  
GGG ACC GTG CAC CTC TCC TGC CAG GAG AAA CAG AAC ACC GTG  
TGC ACC TGC CAT GCA GGT TTC TTT CTA AGA GAA AAC GAG TGT  
GTC TCC TGT AGT AAC TGT AAG AAA AGC CTG GAG TGC ACG AAG  
TTG TGC CTA CCC CAG ATT GAG AAT; and

C) a fragment or variant of A or B.

D  
cont.  
41. A polypeptide according to claim 40, wherein said polypeptide is encoded by DNA comprising the sequence:

R<sup>2</sup> GAT AGT GTG TGT CCC CAA GGA AAA TAT ATC CAC CCT CAA  
AAT AAT TCG ATT TGC TGT ACC AAG TGC CAC AAA GGA ACC TAC  
TTG TAC AAT GAC TGT CCA GGC CCG GGG CAG GAT ACG GAC TGC  
AGG GAG TGT GAG AGC GGC TCC TTC ACC GCT TCA GAA AAC CAC  
CTC AGA CAC TGC CTC AGC TGC TCC AAA TGC CGA AAG GAA ATG  
GGT CAG GTG GAG ATC TCT TCT TGC ACA GTG GAC CGG GAC ACC  
GTG TGT GGC TGC AGG AAG AAC CAG TAC CGG CAT TAT TGG AGT  
GAA AAC CTT TTC CAG TGC TTC AAT TGC AGC CTC TGC CTC AAT  
GGG ACC GTG CAC CTC TCC TGC CAG GAG AAA CAG AAC ACC GTG  
TGC ACC TGC CAT GCA GGT TTC TTT CTA AGA GAA AAC GAG TGT  
GTC TCC TGT AGT AAC TGT AAG AAA AGC CTG GAG TGC ACG AAG  
TTG TGC CTA CCC CAG ATT GAG AAT

wherein R<sup>2</sup> is absent or is a DNA comprising a sequence coding for a polypeptide which can be cleaved *in vivo*, or a fragment or variant thereof.

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42. A polypeptide according to claim 41, wherein R<sup>2</sup> is a DNA comprising a sequence which codes entirely or partly for a signal sequence.
43. A polypeptide according to claim 41, wherein R<sup>2</sup> is a DNA comprising the sequence CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA or a fragment or variant thereof.
44. A polypeptide according to claim 42, wherein R<sup>2</sup> is a DNA comprising the sequence R<sup>3</sup> CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA, wherein R<sup>3</sup> is a DNA coding for a signal peptide, or a fragment or variant thereof.
- D  
cont.*
45. A polypeptide according to claim 44, wherein R<sup>3</sup> is a DNA comprising the sequence:
- ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG CTG CCA CTG GTG  
CTC CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA GGG GTT ATT  
GGA, or
- or a fragment or variant thereof.
46. A recombinant polypeptide encoded by a nucleic acid which hybridizes with DNA complementary to the DNA defined in claim 40 under conditions of low stringency and said polypeptide has the ability to bind TNF.

47. A recombinant polypeptide having the ability to bind TNF selected from the group consisting of:

A) a polypeptide comprising the amino acid sequence:

met gly leu ser thr val pro asp leu leu leu pro leu val  
leu leu glu leu leu val pro his leu gly asp ile tyr pro ser pro gly val ile  
gly leu val pro his leu gly asp arg glu lys arg asp asn asn asp ser  
val cys pro gln gly lys tyr ile his pro gln asn asn asp ser  
ile cys cys thr lys cys his lys gly thr tyr leu tyr asn  
asp cys pro gly pro gly gln asp thr asp cys arg glu cys  
glu ser gly ser phe thr ala ser glu asn his leu arg his  
cys leu ser cys ser lys cys arg lys glu met gly gln val  
glu ile ser ser cys thr val asp arg asp thr val cys gly  
cys arg lys asn gln tyr arg his tyr trp ser glu asn leu  
phe gln cys phe asn cys ser leu cys leu asn gly thr val  
his leu ser cys gln glu lys gln asn thr cys thr cys  
his ala gly phe phe leu arg glu asn glu cys val ser cys  
ser asn cys lys lys ser leu glu cys thr lys leu cys leu  
pro gln ile glu asn val lys gly thr glu asp ser gly thr  
thr val leu leu pro leu val ile phe phe gly leu cys leu  
leu ser leu leu phe ile gly leu met tyr arg tyr gln arg  
trp lys ser lys leu tyr ser ile val cys gly lys ser thr  
pro glu lys glu gly glu leu glu gly thr thr lys pro  
leu ala pro asn pro ser phe ser pro val pro ser pro  
pro thr leu gly phe ser pro val pro ser ser thr phe thr  
ser ser ser thr tyr thr pro gly asp cys pro asn phe ala  
ala pro arg arg glu val ala pro pro tyr gln gly ala asp  
pro ile leu ala thr ala leu ala ser asp pro ile pro  
pro leu gln lys trp glu asp ser ala his lys pro gln ser  
leu asp thr asp asp pro ala thr leu tyr ala val val glu  
asn val pro pro leu arg trp lys glu phe val arg arg leu  
gly leu ser asp his glu ile asp arg leu glu leu gln asn  
gly arg cys leu arg glu ala gln tyr ser met leu ala  
trp arg arg arg thr pro arg arg glu ala thr leu glu leu  
leu gly arg val leu arg asp met asp leu leu gly cys leu  
glu asp ile glu glu ala leu cys gly pro ala ala  
pro ala pro ser leu leu arg;

B) a polypeptide comprising the amino acid sequence:

asp ser val cys pro gln gly lys tyr ile his pro gln asn  
asn ser ile cys cys thr lys cys his lys gly thr tyr leu  
tyr asn asp cys pro gly pro gly gln asp thr asp cys arg  
glu cys glu ser gly ser phe thr ala ser glu asn his leu  
arg his cys leu ser cys ser lys cys arg lys glu met gly  
gln val glu ile ser ser cys thr val asp arg asp thr val  
cys gly cys arg lys asn gln tyr arg his tyr trp  
ser glu asn leu phe gln cys phe asn cys ser leu cys leu  
asn gly thr val his leu ser cys gln glu lys gln asn thr  
val cys thr cys his ala gly phe leu arg glu asn glu  
cys val ser cys ser asn cys lys ser leu glu cys thr  
lys leu cys leu pro gln ile glu asn; and

C) a fragment, variant, or functional derivative of A or B.

*P cont.*  
48. A polypeptide according to claim 47, wherein said polypeptide is selected from the group consisting of:

a polypeptide comprising the amino acid sequence:

R<sub>2</sub> asp ser val cys pro gln gly lys tyr ile his pro gln asn  
asn ser ile cys cys thr lys cys his lys gly thr tyr leu  
tyr asn asp cys pro gly pro gly gln asp thr asp cys arg  
glu cys glu ser gly ser phe thr ala ser glu asn his leu  
arg his cys leu ser cys ser lys cys arg lys glu met gly  
gln val glu ile ser ser cys thr val asp arg asp thr val  
cys gly cys arg lys asn gln tyr arg his tyr trp  
ser glu asn leu phe gln cys phe asn cys ser leu cys leu  
asn gly thr val his leu ser cys gln glu lys gln asn thr  
val cys thr cys his ala gly phe leu arg glu asn glu  
cys val ser cys ser asn cys lys ser leu glu cys thr  
lys leu cys leu pro gln ile glu asn;

wherein R<sub>2</sub> is absent or is a polypeptide which can be cleaved *in vivo*; and  
a fragment, variant, or functional derivative thereof which binds TNF.

*E* 49. A polypeptide according to claim 48, wherein said polypeptide includes at least one additional amino acid at the amino-terminus, at the carboxyl-terminus, or at both the amino-terminus and at the carboxyl-terminus.

*16* 50. A polypeptide according to claim 49, wherein said polypeptide includes at least one additional amino acid at the amino-terminus and at the carboxyl-terminus.

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cont.* 51. A polypeptide according to claim 49, wherein said polypeptide includes at least one additional amino acid at the amino-terminus.

*18* 52. A polypeptide according to claim 51, wherein said polypeptide includes a methionine at the amino-terminus.

*19* 53. A polypeptide according to claim 49, wherein said polypeptide includes at least one additional amino acid at the carboxyl-terminus.

54. A polypeptide according to claim 48, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution, insertion, or deletion in the sequence of claim 48.
55. A polypeptide according to claim 40, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution, insertion, or deletion in the sequence of claim 48.
56. A polypeptide according to claim 50, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution, insertion, or deletion in the sequence of claim 48.
57. A polypeptide according to claim 51, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution, insertion, or deletion in the sequence of claim 48.
58. A polypeptide according to claim 52, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution, insertion, or deletion in the sequence of claim 48.

59. A polypeptide according to claim 53, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution, insertion, or deletion in the sequence of claim 48.
60. A polypeptide according to claim 54, wherein said polypeptide is a variant having at least one intrasequence amino acid insertion in the sequence of claim 48.
61. A polypeptide according to claim 54, wherein said polypeptide is a variant having at least one intrasequence amino acid deletion in the sequence of claim 48.
62. A polypeptide according to claim 54, wherein said polypeptide is a variant having at least one intrasequence amino acid substitution in the sequence of claim 48.
63. A polypeptide according to claim 62, wherein said polypeptide includes a methionine at the amino-terminus.
64. A polypeptide according to claim 62, wherein said polypeptide includes a methionine at the amino-terminus and said amino acid substitution is at a glycosylation site.

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65. A polypeptide according to claim 62, wherein said amino acid substitution is at a glycosylation site.
66. A recombinant polypeptide encoded by a nucleic acid that hybridizes to a DNA complementary DNA encoding the amino acid sequence defined in claim 48 under conditions of low stringency and said polypeptide has the ability to bind TNF.
- ord  
E 33 67. A pharmaceutical composition comprising a polypeptide of claim 40 and a pharmaceutically acceptable carrier.
- E 34 68. A pharmaceutical composition comprising a polypeptide of claim 48 and a pharmaceutically acceptable carrier.--
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#### REMARKS

Applicants canceled claims 19 to 21 without prejudice or disclaimer. Applicants amended claim 27 above. Applicants also added claims 40-68 above. Claims 27 to 30 were added November 18, 1996, and claims 31 to 39 were added April 29, 1997. Claims 24 and 27 to 68 are pending.

#### 1. Objection To Claim 2

The Examiner contended that claim 2 was improper since it included the term "optionally." Office Action at page 2, Item No. 1. The Examiner asserted that a Board